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## **Pendrin – a new target for diuretic therapy ?**

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Diuretics are among the most frequently used drugs to treat hypertension, congestive heart failure, edema, and play a role in the prevention of some forms of recurrent nephrolithiasis <sup>1-3</sup>. Most commonly used diuretics act by directly inhibiting tubular transport processes such as the loop diuretics blocking the  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  -cotransporter NKCC2 in the thick ascending limb of the loop of Henle, the thiazides and chlortalidones inhibiting the  $\text{Na}^+/\text{Cl}^-$  -cotransporter NCC in the distal convoluted tubule, or the potassium-sparing diuretics of the amiloride or triamterene type blocking the epithelial sodium channel ENaC in the connecting tubule and collecting duct. Other classes of diuretics interfere with metabolic or endocrine mechanisms linked to tubular transport processes such as in the case of the rather infrequently used carbonic anhydrase inhibitors (e.g. acetazolamide) that mostly reduce  $\text{Na}^+/\text{H}^+$  exchanger activity, and the more widely used mineralocorticoid receptor blockers (e.g. spironolactone, eplerenone) reducing the stimulatory effect of aldosterone on ENaC mediated salt absorption. Two novel classes of substances increase diuresis but do not act primarily on salt reabsorptive pathways: the aquaretics blocking the V2 vasopressin receptor reducing AQP2 activation by the antidiuretic hormone (e.g. tolvaptan) and the inhibitors of the SGLT2  $\text{Na}^+/\text{glucose}$  transporter (e.g. canagliflozin, dapagliflozin, and empagliflozin) primarily reducing proximal tubular glucose absorption causing osmotic diuresis <sup>4-5</sup>.

The use of diuretics from the first group directly blocking salt reabsorption can be limited by hypo- or hyperkalemia or hypercalcemia. In CKD patients with increasingly lower GFR, the efficacy of drugs can be reduced requiring escalating doses or alternative drugs. The indication for SGLT2 inhibitors and vasopressin receptor antagonists are distinct and currently mostly restricted to the treatment of type 2 diabetes, ADPKD, or hyponatremic syndromes, respectively. Moreover, the efficacy of diuretics blocking salt absorptive pathways is often limited by the plasticity of the renal tubule and its ability to stimulate the growth and activity of downstream segments contributing to treatment-resistant hypertension <sup>3, 6</sup>. Then combinations of diuretics acting in subsequent segments and on distinct pathways may help to improve diuretic efficacy.

The collecting duct is the last site of salt reabsorption and contributes to up to 2 % of absorption of the filtered salt load. Renal salt reabsorption in the collecting duct depends on several factors and transport pathways. Distal delivery of sodium

and chloride is determined by glomerular filtration rate and the rate of reabsorption of both ions in upstream nephron segments. Particularly, NaCl reabsorption by the thick ascending limb of the loop of Henle and by the distal convoluted tubule influences the delivery of sodium and chloride to the collecting duct. There, sodium is reabsorbed in part by the epithelial Na<sup>+</sup>-channel ENaC which is stimulated by angiotensin II and aldosterone. Chloride absorption occurs via different routes, in part through the paracellular pathway requiring claudins 4 and 8 and through intercalated cells <sup>7-8</sup>. In non-type A intercalated cells chloride can be directly reabsorbed in exchange for bicarbonate, a process mediated by the anion exchanger pendrin, or chloride absorption can be coupled to sodium absorption involving a more complex scheme. Secretion of 2 bicarbonate and absorption of 2 chloride ions by pendrin is driving the activity of another transporter, NDBCE (Na<sup>+</sup>-dependent bicarbonate-chloride exchanger), exchanging one intracellular chloride for one extracellular bicarbonate plus one sodium (figure 1). This results in the net absorption of NaCl <sup>8</sup>.

Insights into the relevance of pendrin in renal salt handling come from human genetics studying patients with the rare Pendred syndrome and from various mouse models. Patients with Pendred syndrome due to mutations in pendrin (SLC26A6) suffer most notably from sensorineural deafness and frequently develop hypothyroidism and goiter. However, their renal phenotype has been studied very little to date. Hypochloremic alkalosis was reported in two cases with Pendred syndrome; however, the condition occurred only during acute illness or therapy with thiazides primarily causing volume depletion <sup>9-10</sup>. Next to these incidental reports, detailed studies in mice suggest an important role of pendrin in renal control of salt excretion and blood pressure. Salt depletion or aldosterone stimulate pendrin expression and activity in parallel to other chloride and sodium transport proteins such as NaCl cotransporter NCC or the epithelial sodium channel ENaC <sup>8</sup>. Mice lacking pendrin lose more salt during salt depletion and have lower blood pressure suggesting that pendrin is required for the renal capacity to conserve salt and maintain blood pressure. Moreover, pendrin deficient mice are partly protected from developing hypertension during high salt/ aldosterone treatment. Vice versa, mice overexpressing pendrin develop chloride sensitive hypertension <sup>11</sup>.

Since salt absorption by the collecting duct is influenced by salt delivery, the role of pendrin in compensating for reduced salt absorption by earlier segments has

been studied. On the one hand, chronic inhibition of NCC activity with thiazides increases pendrin expression whereas on the other hand concomitant genetic ablation of NCC and pendrin causes a severe syndrome of renal salt loss and volume depletion<sup>8, 12</sup>. Similarly, deletion of NCC and the NDBCE transporter working in conjunction with pendrin leads also to salt wasting<sup>13</sup>. Taken together, the biology of pendrin and its interactions with other salt transporting pathways make pendrin an attractive target for novel inhibitors that may be useful as diuretics standing alone or used in combination with existing drugs to enhance their efficacy.

Alan Verkman and colleagues identified novel compounds selectively inhibiting pendrin with high affinity using a functional chemical library screen<sup>14</sup>. As reported here in this issue of JASN, these compounds given to mice had *per se* no effect on diuresis or acid-base parameters in urine and blood. However, when given in combination with furosemide, pendrin inhibitors potentiated the diuretic effect of furosemide. Importantly, the pendrin inhibitor even further increased diuresis in mice given chronically furosemide. On the other hand, mice treated with hydrochlorothiazide plus pendrin inhibitor showed a paradoxical reduction in diuresis<sup>15</sup>.

Several issues are of major interest and some questions remain open. Next to tests of safety and pharmacokinetics in humans, the question remains whether pendrin inhibitor will have a similar diuretic potency in humans as in rodents. The relative number of pendrin expressing cells may be relatively lower in human kidney compared to rodent kidney and may thus limit its efficacy<sup>16-17</sup>.

Next to kidney, pendrin (SLC26A4) is expressed in various other organs including thyroid glands, inner ear, adrenal glands, and airways which will impact on its side effects as well modulate its diuretic and anti-hypertensive effects. While pendrin function in inner ear and thyroid glands may be problematic and may cause side effects, the inhibition of adrenal gland pendrin may add to the beneficial effects of pendrin blockade in kidney. Pendrin function in adrenal glands appears to support aldosterone secretion and inhibition may help to reduce renal salt reabsorption as well as other extrarenal effects of aldosterone, e.g. in heart and vasculature<sup>18</sup>.

Chronic treatment with loop diuretics as well as with thiazides and chlortalidones often cause hypokalemia due to the excessive stimulation of

potassium secretion in the collecting duct by increased urinary flow and stimulation of ENaC activity which in turn increases ROMK mediated  $K^+$ -secretion. The combination of the pendrin inhibitor with furosemide further increased urinary  $K^+$ -excretion pointing to another possible side effect of this class of inhibitors. Also metabolic alkalosis was aggravated by the combination of furosemide and the pendrin inhibitor further underlining the potency of this combination.

The pendrin inhibitor reduced the diuretic response to thiazide treatment. At first glance this is surprising since the combined ablation of NCC and pendrin causes a massive diuresis and renal phenotype in mice <sup>12</sup>. However, thiazides have also been reported to block not only NCC activity but also the NDCBE transporter working in conjunction with pendrin in the collecting duct. Thus, during acute treatment with thiazides, both NCC and NDCBE/pendrin dependent salt absorption may be blocked and further blockade with a pendrin inhibitor does not cause more salt wasting. In contrast, pendrin inhibition in adrenal glands may reduce filtration and thereby cause a paradoxical reduction in diuresis. Clearly, these effects will require more clarification and may also provide novel insights into the renal handling of chloride and the role of pendrin.

Pendrin inhibitors, if making the difficult way into clinics, may represent another promising new class of drugs targeting a tubular transport pathway like the more recently developed inhibitors of urea transporters or the renal ROMK potassium channel <sup>19-20</sup>. Their specific application may be in the combination with other diuretics such as loop diuretics to address some of the adaptive responses of the tubular transport machinery contributing to the resistance to diuretics.

## Figure legend

### **Figure 1: Transport pathways involved in salt absorption by the distal convoluted tubule and collecting system as targets of diuretics**

Scheme of a nephron depicting the major transport pathways targeted by commonly used diuretics: In the thick ascending limb of the loop of Henle (TAL), furosemide and chlortalidon inhibit the NKCC2 cotransporter and in the distal convoluted tubule (DCT) thiazides block the NCC cotransporter. In the collecting system (first cells

starting in the late DCT) potassium-sparing diuretics inhibit ENaC activity in principal cells (PC). Chloride absorption occurs in part through a pendrin-dependent process located in type B intercalated cells (B-IC) (basolateral V-ATPase) and non-type A/non-type B intercalated cells (non-A/non-B IC)(apical V-ATPase). V-ATPase driven proton secretion energizes chloride/bicarbonate exchange by pendrin. Coupling of pendrin activity to the Na<sup>+</sup>-dependent chloride/bicarbonate exchanger NDCBE allows for NaCl absorption. NDBCE may also be targeted by thiazides whereas pendrin can be blocked by novel inhibitors.

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Figure 1

